Anemia and Transfusion Medicine

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KEYWORDS

• Perioperative anemia • Transfusion medicine • Pre-operative anemia
• Anemia and surgery

KEY POINTS

- Peri-operative anemia is highly prevalent and remains an independent predictor for post-operative mortality and morbidity.
- Pre-operative evaluation should focus on identifying the cause of anemia and optimization strategies should focus on increasing red cell mass and correcting any nutritional deficiencies.
- Intravenous iron is safe and can be used for correcting pre-operative and post-operative anemia, especially when iron deficiency anemia is present.
- International normalized ratio should not be used as the sole measure of coagulopathy when considering reversal strategies as it may not accurately reflect thrombin generation and actual hemostasis.

EPIDEMIOLOGY AND MORBIDITY OF PERIOPERATIVE ANEMIA

Anemia is a condition where the number of red blood cells (RBCs) or the hemoglobin (Hgb) concentration within them is lower than normal. World Health Organization (WHO) defines anemia as Hgb as less than 12 g/dL in non-pregnant women, less than 11 g/dL in pregnant women and less than 13 g/dL in men.[1] Globally, there were 1.76 billion prevalent cases of anemia in 2019.[2]

Peri-operative anemia is a common condition encountered in adult surgical patients. It is increasingly recognized as a predictor of post-operative morbidity and mortality. Additionally, patients with perioperative anemia have increased risk of infection and length of stay (LOS) leading to increased resource utilization.[3,4] Pre-operative anemia is the number one predictor for the need for perioperative RBC transfusion. RBC transfusion, in turn, can have many downstream complications including risks

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from ABO incompatibility, transfusion reactions, infections, circulatory overload, and acute lung injury. The estimates of pre-operative anemia are highly variable based on the literature with a range from 5% to 75%.[5] In post-operative patients, this number can be as high as 90%.[5] Women tend to have higher risk of post-operative anemia as they have low circulating blood volume compared with men, so the same amount of blood loss leads to a more significant effect on the loss of blood volume that may lead to higher transfusion rates in women.[6] Therefore, in perioperative settings, a target Hgb of greater than 13 g/dL should be considered irrespective of sexes.[7,8]

With an aging surgical population, the prevalence of anemia in elderly patients is of considerable importance. A retrospective study of 310,311 elderly veterans with pre-operative anemia demonstrated that every percentage-point decrease in pre-operative hematocrit value below 39% was associated with a 1.6% increased 30-day postoperative mortality.[9] Another study of elderly patients (age >65 years) using prospective American College of Surgeons National Surgical Quality Improvement Program database of 31,857 patients undergoing elective vascular surgery found that 47% of the study population was anemic.[10] Patients with anemia had significantly higher rates of cardiac events and post-operative mortality leading authors to conclude that identification and treatment of anemia should be important components of pre-operative care for patients undergoing vascular operations.[10]

A retrospective study of 7759 non-cardiac surgery patients showed about 40% prevalence of preoperative anemia, which was in turn associated with a nearly 5-fold increase in the odds of post-operative mortality.[11] A systematic review of orthopedic hip and knee surgeries showed that perioperative anemia was associated with a blood transfusion rate of 45 $\pm$ 25% and 44 $\pm$ 15%, post-operative infections, poorer physical functioning and recovery, and increased LOS and mortality.[12] Sequeira and colleagues conducted a study of iron deficiency anemia (IDA) using national insurance database of patients who underwent Total Hip Arthroplasty (THA) between 2005 and 2014 evaluating rates of post-operative medical complications, surgery-related complications, hospital readmission, emergency department visits, and mortality.[13] Additionally, 90-day and day of surgery cost and LOS were calculated.[13] In total, 98,681 patients with a pre-operative diagnosis of IDA who underwent THA were identified and compared with 386,724 controls. Not only was IDA associated with increased risk of 30-day emergency department visits and 30-day readmission but also IDA was also associated with an increased 90-day medical complication rate, 1-year periprosthetic joint infection, revision, dislocation, and fracture. Patients with IDA accrued higher hospital charges ($27,658.27 vs $16,709.18, P<.001) and lower hospital reimbursement ($5509.90 vs $3605.59, P<.001) while evaluating the economic impact.[13] One may conclude that severe anemia is responsible for adverse post-operative outcomes, but in a retrospective study of 227,425 non-cardiac surgery patients, even mild anemia (hematocrit between 38%–28% in men and 35%–28% in women) was independently associated with increased 30-day morbidity and mortality.[14]

An important goal of pre-operative anemia optimization is to increase hemoglobin levels enough to avoid blood transfusion. Another outcome that must be prevented is the development of myocardial ischemia. Recently in the non-cardiac surgery population, peri-operative anemia correlates with an increased risk of myocardial ischemia in non-cardiac surgery (MINS). A retrospective cohort analysis of 6141 patients, from which 4480 were evaluated, demonstrated MINS in 155 patients (incidence of 3.5%) in the overall cohort; the incidence was 0% among patients whose postoperative hemoglobin was greater than 13 g/dL and it rose up to 8.5% among patients whose minimum post-operative hemoglobin was less than 8 g/dL. The risk for developing MINS was 1.29 [HR 1.29, 95% CI 1.16–1.42; P<.001] for every 1 g/dL

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decrease in post-operative hemoglobin in both time-varying covariate analysis and sensitivity analyses.[15] Another single center retrospective study of 35,170 patients comparing 22,062 (62.7%) patients with normal hemoglobin versus 13,108 (37.3%) with post-operative anemia in whom 11,919 sets of patients were analyzed with propensity score matching, demonstrated a higher incidence of MINS among patients with anemia [14.5 versus 21.0%, (OR) 1.57, 95% CI 1.47–1.68; *P*<.001]. The estimated threshold for pre-operative hemoglobin associated with MINS was 12.2 g/dL (AUC 0.622).[16]

EVALUATION OF PERIOPERATIVE ANEMIA

Anemia is a single marker for adverse peri-operative outcomes, especially in elderly patients.[14,17–20] Therefore, once identified, an appropriate evaluation for the etiology of anemia pre-operatively must be pursued, to optimize Hgb values with non-transfusion interventions, which subsequently decreases the risk of adverse outcomes and receiving allogeneic blood product transfusions in the peri-operative period.

Peri-operative blood management and optimization include correction of coagulopathy, source control of hemorrhage, enhancement of patient's tolerance to anemia, as well as improving the hemoglobin and hematocrit.[21] However, the modifiable risk factors that can be corrected without transfusion of blood products are often nutritional (hematinic) deficiencies, which include mostly iron, cyanocobalamin (vitamin B12), and folic acid. Zinc and copper deficiencies can also cause refractory anemia and must be considered.[22,23] Also, hematinic deficiency even in patients without anemia are associated with adverse outcomes. Among patients undergoing cardiac surgery, even those who are not anemic, the presence of iron deficiency was correlated with adverse outcomes, and therefore, its pre-operative optimization enhances overall prognosis.[24]

There are multiple algorithms designed to evaluate anemia. The authors propose a simplified, yet comprehensive algorithm that allows one to evaluate anemia (Hb < 13 g/dL irrespective of gender) pre-operatively (**Fig. 1**). A detailed history is fundamental. It should include: history or symptoms of anemia, transfusion history, history of

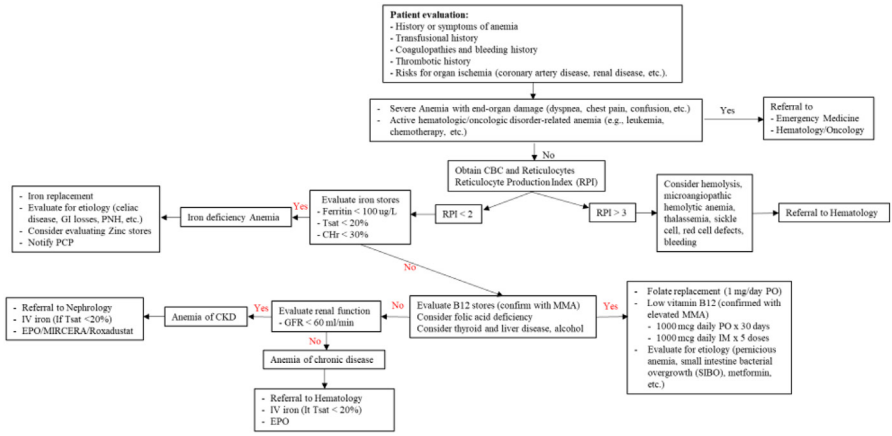
Patient evaluation:
- History or symptoms of anemia
- Transfusional history
- Coagulopathies and bleeding history
- Thrombotic history
- Risks for organ ischemia (coronary artery disease, renal disease, etc.).
- Severe Anemia with end-organ damage (dyspnea, chest pain, confusion, etc.)
- Active hematologic/oncologic disorder-related anemia (e.g., leukemia, chemotherapy, etc.)
Yes
Referral to
- Emergency Medicine
- Hematology/Oncology
No
Obtain CBC and Reticulocytes
Reticulocyte Production Index (RPI)
RPI < 2
RPI > 3
Consider hemolysis, microangiopathic hemolytic anemia, thalassemia, sickle cell, red cell defects, bleeding
Referral to Hematology
Evaluate iron stores
- Ferritin < 100 ug/L
- Tsat < 20%
- CHr < 30%
Yes
Iron deficiency Anemia
- Iron replacement
- Evaluate for etiology (celiac disease, GI losses, PNH, etc.)
- Consider evaluating Zinc stores
- Notify PCP
No
Evaluate B12 stores (confirm with MMA)
Consider folic acid deficiency
Consider thyroid and liver disease, alcohol
Yes
- Folate replacement (1 mg/day PO)
- Low vitamin B12 (confirmed with elevated MMA)
- 1000 mcg daily PO x 30 days
- 1000 mcg daily IM x 5 doses
- Evaluate for etiology (pernicious anemia, small intestine bacterial overgrowth (SIBO), metformin, etc.)
No
Evaluate renal function
- GFR < 60 ml/min
Yes
Anemia of CKD
- Referral to Nephrology
- IV iron (If Tsat <20%)
- EPO/MIRCERA/Roxadustat
No
Anemia of chronic disease
- Referral to Hematology
- IV iron (It Tsat < 20%)
- EPO

Fig. 1. Algorithm for evaluation and optimization of pre-operative anemia (Hb < 13 g/dL). (*Adapted from* Warner MA, Shore-Lesserson L, Shander A, Patel SY, Perelman SI, Guinn NR. Perioperative Anemia: Prevention, Diagnosis, and Management Throughout the Spectrum of Perioperative Care. Anesth Analg. 2020 May;130(5):1364-1380. https://doi.org/10.1213/ANE.0000000000004727. PMID: 32167979.)

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coagulopathies, and bleeding, as well as thrombosis, in addition to the risk factors for end organ ischemia (coronary artery disease, renal disease, and so forth.).[25,26] The pre-operative optimization will focus mostly on stable patients in whom there is opportunity to optimize the anemia. Patients with severe anemia with end-organ damage (dyspnea, chest pain, confusion, and so forth.), as well as with active hematologic-oncologic disorder-related anemia (eg, leukemia, chemotherapy, and so forth.) should be referred to a hematologist.[26]

The reticulocyte production index (RPI) allows differentiation of hypoproliferative from hyperproliferative conditions. Elevated RPI (>3) points most commonly to underlying hemolysis, and therefore, formal Hematology referral is warranted.[5,25,26]

In the preoperative realm, it is hypoproliferative anemia (RPI < 2) that the authors focus most given that its etiology is often secondary to nutritional deficiencies and therefore, can be corrected with supplementation. Since the most common nutritional deficiency associated with anemia is iron deficiency,[27] the algorithm starts with formal assessment of iron stores. This includes measurement of transferrin saturation, ferritin levels, and reticulocyte hemoglobin content (CHr). Iron deficiency is defined by ferritin less than 100 μg/L, transferrin saturation less than 20%, or CHr less than 30%.[26] Less common nutritional deficiency causes of anemia include copper and zinc deficiency, the latter being more common; in our practice, formal evaluation for zinc deficiency is done, especially among patients with low alkaline phosphatase, and if identified, replacement is recommended.[28]

If the iron stores are normal, then the focus of evaluation shifts toward identifying cyanocobalamin deficiency, confirming it with elevated methylmalonic acid. Folic acid deficiency must also be considered; however, its evaluation is considered not essential as it can be easily supplemented both enterally and parenterally with rapid correction of stores.[29] As with other hematinic deficiencies, formal identification of underlying etiology is warranted for long-term optimization.

In patients in whom no significant hematinic levels deficiencies are found, then consider identifying anemia of chronic inflammation and anemia of chronic renal disease.

OPTIMIZATION OF ANEMIA

Anemia is often a sign of underlying disease. Therefore, the first step in anemia optimization is to identify and treat the disease that is causing anemia, as discussed previously. Once the etiology of anemia has been identified and treated, best practice is to try to optimize anemia before any major surgery.

Optimizing Iron Deficiency Anemia

Given that IDA is the most common etiology of anemia in surgical patients, there have been multiple studies assessing outcomes of treatment of IDA before surgery. These studies have looked at both oral and intravenous (IV) iron use and their role in reducing blood transfusions or other post-operative complications.

Oral iron: Oral iron replacement is cheap and easily available, but the effectiveness is reduced by poor absorption and gastrointestinal side effects like constipation, diarrhea, abdominal discomfort, and metallic taste. Multiple formulations are available (**Table 1**); the authors suggest ferrous sulfate given its broader availability and cost. Non-adherence to daily iron has been estimated to range from 10% to 32%.[30] Intestinal bacterial overgrowth in metabolic syndrome, uremia and chronic use of antacids, calcium supplements and, prior gastric bypass surgery have all been shown to reduce absorption of key nutrients in the intestine, including iron.[31] Furthermore, it can take 3–6 months to completely replenish iron stores depending on the severity of IDA.

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Table 1
Oral iron formulations

Formulation	Elemental Iron Content/Tab
Ferric citrate	210 mg/g
Ferric maltol	30 mg/30 mg
Ferrous fumarate	106 mg/324 mg
Ferrous gluconate	27 mg/240 mg; 38 mg/324 mg
Ferrous sulfate	65 mg/325 mg
Ferric pyrophosphate	120 mg/g
Polysaccharide iron complex	Variable over the counter-eg, 50 mg/50 mg
Carbonyl iron	1000 mg/g

Although it may be reasonable to delay some elective surgeries, like THA, to allow complete replenishment of iron stores; other time sensitive surgeries, like those for cancer, cannot be delayed. If oral iron is used for repletion, the recommended dose is 60 mg to 120 mg of elemental iron per day. Of this dose, there is wide variation in the percentage absorbed ranging from 2% to 30% depending on food intake or not. It is recommended to periodically check Hgb during this time to assess response. Recent data provide evidence that higher daily dosages of iron can increase hepcidin activity that will in turn decrease enteral iron absorption through its effect on the ferroportin pathway.[32] A randomized trial to study alternate day dosing versus daily dosing found that providing iron supplements on alternate days and in single doses optimizes iron absorption and might be a preferable dosing regimen.[33,34] In another randomized study of 200 adults with IDA comparing alternate day single 120 mg dose iron sulfate to daily single 60 mg dose found no significant difference in Hgb improvement at 8 weeks.[30] A guide to commonly available oral iron formulations is shown in **Table 1**. If Hgb checked 4 weeks before surgery shows no response to oral iron despite compliance, then IV iron should be recommended.

Parenteral iron: Parenteral or IV iron has traditionally been reserved as a last resort because of its cost and associated risk of adverse reactions. However, the newer formulations have much improved safety profile and, with increased awareness, it is being widely accepted as a superior treatment option when compared with oral iron. IV iron has a superior bioavailability compared with oral iron. The currently available IV iron formulations and their recommended dosages are shown in **Table 2**. IV iron is especially useful in patients with functional iron deficiency where chronic inflammation often leads to poor enteral absorption of oral iron. IV iron also allows for a faster response as seen with Hgb improvement as early as 5 days to at most 3 weeks after infusion.[35] This can be a crucial factor in decision making when surgery cannot be significantly delayed.

The evidence on the benefit of IV iron on reduction of blood utilization and other post-operative complications has, so far, been mixed. In a randomized controlled trial of patients undergoing major abdominal surgery, 72 patients with IDA were enrolled and given either IV iron or placebo.[36] A 60% reduction in allogeneic blood transfusion and shorter LOS was observed in IV iron group. There was no difference in morbidity, mortality, or quality of life between IV iron and placebo.[36] But another well-conducted randomized trial evaluating IV iron infusion versus placebo before major abdominal surgery did not reveal a benefit towards transfusion reduction or mortality.[37] The pre-operative IV iron to treat anemia before major abdominal surgery trial, which was a double-blind randomized controlled trial in 487 adult patients with pre-operative anemia undergoing elective major open abdominal surgery who were randomized to

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Table 2
Different intravenous iron formulations currently approved for use in the United States[45]

Generic Name	US Brand Name	Plasma Half Life (hr)	Need for Test Dose	Single Total Dose Infusion	Suggested Dosage and Frequency (for 1000 mg Deficit)
Iron Dextran	Infed	20	Yes	Yes	25 mg test dose followed by 1000 mg single dose.
Sodium Ferric Gluconate	Ferrlecit	1	No	No	125 mg IV daily up to 8 doses.
Iron Sucrose	Venofer	6	No	No	200 mg daily up to 5 doses.
Ferumoxytol	Feraheme	15	No	No	510 mg every 3–8 d for 2 doses.
Ferric Carboxymaltose	Injectafer	16	No	No	15 mg/kg every 7 d for 2 doses.
Ferric Derisomaltose (Iron isomaltoside)	Monoferric	20	No	Yes	1000 mg single dose.

Adapted from Kalra SK TB, Khambaty M, Manjarrez E. Post-operative Anemia After Major Surgery: a Brief Review. Current Emergency and Hospital Medicine Reports. 16 June 2021 2021;9: 89–95.

receive IV iron (244) or placebo (243) 10 days to 42 days before surgery. End points were risk of the composite outcome of blood transfusion or death and number of blood transfusions from randomization to 30 days post-operatively. There was no superiority of IV iron versus placebo to decrease the need for blood transfusion (RR 0.98, 95% CI 0.68–1.43; P=.93).[37] There was a significant trend for reduced readmissions in this trial raising the possibility of benefit of IV iron in post-operative recovery. Nonetheless, the results from this study reinforced the findings from a 2019 Cochrane review of 6 randomized controlled trials of 372 anemic patients, which did not reveal a benefit in reducing red cell transfusions in patients who were treated with pre-operative oral, or IV iron supplementation compared with no treatment, placebo, or usual care.[38] On the other hand, a recent meta-analysis of randomized trials using preoperative IV iron compared with oral iron or placebo in colorectal surgery patients showed that use of IV iron reduced the risk of blood transfusion compared with oral iron or placebo. There was no mortality difference between the groups.[39]

Studies have also evaluated the benefit of erythrocyte stimulating agents (ESAs) and IV iron used concurrently. In patients with anemia and iron deficiency, preoperative treatment with a single dose of IV ferric derisomaltose and darbepoetin decreased the proportion of participants who received a peri-operative blood transfusion compared with treatment with oral ferrous sulphate.[40] In a prospective randomized trial of 1006 patients undergoing cardiac surgery, an ultra-short-term combination treatment with IV iron, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid reduced RBC and total allogeneic blood product transfusions in patients with pre-operative anemia or isolated iron deficiency.[41] IV iron has also been studied in non-anemic iron deficient patients. In a randomized trial of 60 non-anemic cardiac surgery patients, a single peri-operative 1000 mg dose of IV iron isomaltoside significantly increased the Hgb level and prevented anemia 4 weeks after surgery, with a short-term safety profile like placebo.[42]

As noticeable, most of the studies have been in pre-operative setting and there is limited evidence of use of IV iron in post-operative period. A consensus guideline published in 2017 recommended use of IV iron for post-operative anemia.[43] It was

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postulated that post-surgical inflammation is likely to render oral iron ineffective because of increased levels of hepcidin and IV iron can bypass this risk.[43]

Adverse events: Clinicians are often hesitant to use IV iron because of fear of infusion reactions and anaphylaxis. The concern for infusion reactions was evaluated recently in which overall risk for anaphylaxis and other infusion reactions with IV iron formulations was low, especially with newer formulations.[44] In this multicenter cohort, 35,737 IV iron infusions were administered to 12,237 patients, the incidence of infusion reactions was 3.9%, with only 2 total documented epinephrine administrations. Surprisingly, the incidence of adverse events among those who received premedication was 23-fold higher compared with those who did not. However, many patients who received premedication had a prior history of reactions to IV iron.[44]

Despite a lack of level one evidence for the benefit of IV iron, it is still a best practice to replenish iron stores before major surgery, especially those associated with significant blood loss (>300 mL), and the cost of IV iron can potentially be offset by cost saving from reduced transfusion. In summary, the authors recommend an individualized approach with careful consideration of potential risks and benefits before recommending either oral or IV iron therapy.

Optimizing Anemia of Chronic Disease

Anemia of chronic disease is also commonly encountered preoperatively, where patients may have anemia from chronic kidney disease (CKD) or chronic inflammation from an underlying condition. In these conditions, the iron metabolism is also impaired because of ineffective erythropoiesis. Therefore, it is important to assess for concomitant iron deficiency in these patients and to optimize both conditions.

Erythrocyte Stimulating Agents (ESAs): There is insufficient erythropoietin production in patients with CKD that commonly leads to anemia. ESAs have been extensively studied and used in CKD, especially those on dialysis. The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for anemia in CKD suggests initiating ESAs to maintain Hgb of 9.0 g/dL to 10.0 g/dL, with the goal of preventing the Hgb from being less than 9 g/dL. However, individualization of therapy is reasonable as some patients may benefit from initiation of ESAs at a Hgb more than 10 g/dL. For all patients, ESAs should be discontinued if the Hgb exceeds 13 g/dL, and for most patients, ESAs should be stopped when the Hgb is more than 11.5 g/dL.[46] ESAs are currently approved by Food and Drug Administration (FDA) for use in surgical patients to reduce the transfusions in certain major surgery patients. It is beneficial even in non-CKD patients who are anemic and are at risk for significant blood loss during surgery. Studies on use of ESAs have consistently shown a reduction in blood transfusions.[47–50] Of these studies, those in orthopedic surgeries, have shown to have consistent improvement in Hgb with use of ESA along with decreased transfusions. The use of ESAs must be balanced against potential risk of increased thromboembolism risk, and there is FDA advisory to bear caution in patients with heart disease, stroke, and uncontrolled hypertension. Additionally, there is a risk for cancer progression. The 2019 update from American Society of Hematology and Clinical Oncology on the use of ESAs suggested that ESAs can be used in patients with cancer with chemotherapy-induced anemia and low risk of myelodysplastic syndromes.[51] Expert opinion and guidance recommend use in patients who are on chemotherapy with a palliative intent.[51] When ESAs are used pre-operatively, the authors recommend concomitant use of IV iron to prevent patients from developing a functional iron deficiency.

A novel product for anemia optimization in end stage renal disease is Roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor that stimulates

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erythropoiesis and regulates iron metabolism.[52] In renal transplant patients, there is evidence that Roxadustat effectively optimizes anemia and may have renoprotective effects.[53]

Optimizing Other Nutritional Deficiencies

Although IDA is the most common cause of anemia from nutritional deficiencies, there are other vitamins and minerals that are also vital for production of RBC and Hgb. The most important of these include vitamin B12, folic acid, zinc, and copper. Vitamin B12 deficiency takes months to years to develop and manifests with macrocytic and megaloblastic morphology of RBC. Likewise, folate deficiency (although uncommon in US due to fortification of food with folic acid) can lead to macrocytic anemia. In patients with malnutrition, more than one vitamin and mineral deficiency may be present, and the patient may have a normocytic anemia with concomitant deficiency of iron, b12 and folate. B12 deficiency is easily corrected with high dose oral B12, but a careful history should be obtained to rule out malabsorption as the cause of B12 deficiency. In the absence of intrinsic factor, oral B12 is unlikely to be absorbed and injectable form of B12 will be required. Additionally, patients with severe symptomatic anemia from B12 deficiency should also be treated with injectable B12. The authors recommend a weekly 1000 μg intramuscular injection until levels normalize, followed by monthly or every other month maintenance dose administration. When treated appropriately, vitamin B12 deficiency can be corrected within a month. Routine testing of folate levels in patients with anemia has been called into question because of issues around the assays and their reliability.[29] It may be reasonable to treat with folic acid at a dose of 400 μg - 1000 μg when there is a high suspicion for deficiency followed by testing Hgb in 1 week to 2 weeks to measure for an increase in Hgb levels.[29] As discussed earlier, a pragmatic approach of treatment for as little as 1 day before surgery using IV iron, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid has been shown to be effective in reducing RBC transfusion in cardiac surgery patients with pre-operative anemia.[41]

Copper associated anemia is uncommon as most adults get enough copper through their usual diet. Copper deficiency can manifest in times of either increased demand like pregnancy and lactation or low intake as seen with anorexia and malnutrition. Copper is mainly absorbed in stomach and proximal duodenum so malabsorption (inflammatory bowel disease, celiac disease, gastrectomy, bowel resection, and post bariatric surgery) or increased losses (protein losing enteropathy, prolonged diarrhea, and tropical sprue) can also lead to deficiency. Zinc is a competitive inhibitor of oral copper absorption, and excessive zinc consumption can lead to copper deficiency. Iatrogenic deficiency can manifest when parenteral nutrition or enteric nutrition is not supplemented with copper. Copper deficiency affects normal hematopoiesis resulting in anemia and leukopenia. Although the exact mechanism of anemia in copper deficiency is unclear, copper is an important regulator of iron homeostasis. Copper is a vital component in the ferroxidase enzymes, hephaestin and ceruloplasmin. Hephaestus is located in the duodenal mucosa and helps in the oxidation of ferrous iron. Ceruloplasmin is essential for iron transfer from monocyte-macrophage to plasma.[23] Treatment includes oral or IV copper replacement in the form of copper gluconate, copper sulfate, or copper chloride. If concomitant zinc deficiency is present, copper should be repleted first before initiating treatment with zinc.

TRANSFUSION APPROACH TO ANEMIA

There has been a perception that patients may be arbitrarily transfused with hemoglobin thresholds higher than required. Acute normovolemic hemodilution studies

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allowed to recognize in different patient populations, including elderly and stable cardiac patients, tolerance to progressively lower hemoglobin targets without significant adverse outcomes and demonstrating normal cardiovascular response.[54] Subsequently, to evaluate this response in real clinical scenarios, landmark studies were done, demonstrating the tolerance to lower hemoglobin thresholds for transfusion, with similar or even better outcomes when compared with patients transfused at higher hemoglobin thresholds (**Table 3**).

The recommendations for anemia optimization with transfusion of allogeneic blood were recently updated by the Association for the Advancement of Blood & Biotherapies (AABB) and the recommendations are for restrictive transfusion thresholds as below.[70]

- Hemoglobin 7 g/dL
- Hospitalized adult patients who are hemodynamically stable.
- Hospitalized adult patients with hematologic and oncologic disorders.
- Hemoglobin 7.5 g/dL - patients undergoing cardiac surgery.
- Hemoglobin 8 g/dL – patients undergoing orthopedic surgery or those with preexisting cardiovascular disease.

The guidelines did not provide specific recommendations regarding patients with acute coronary syndromes. However, the Myocardial Ischemia and Transfusion (MINT) trial has since been published.[68] This randomized controlled study evaluated 3504 patients, comparing a restrictive transfusion threshold (Hgb 7 or 8 g/dL) with a liberal transfusion threshold (Hgb < 10 g/dL), with the primary outcome being a composite of myocardial infarction or death at 30 days. The primary outcome occurred in 16.9% versus 14.5% (liberal vs restrictive) (RR 1.15; 95% CI, 0.99–1.34; P=.07). Death occurred in 9.9% versus 8.3% (liberal vs restrictive) (RR 1.19; 95% CI, 0.96–1.47) and myocardial infarction occurred in 8.5% versus 7.2% (liberal vs restrictive) (RR 1.19; 95% CI, 0.94–1.49). The authors concluded that although the liberal transfusion strategy did not significantly reduce the outcomes, they could not exclude potential harms of restrictive strategies.[68]

SPECIAL CONSIDERATIONS

Sickle Cell Disease

Patients with sickle cell disease (SCD) undergoing surgery have a higher risk of morbidity and mortality compared with the general population because of risk of sickle cell crisis and chronic organ damage from prior crisis episodes.[71–73] Risks are greater for patients homozygous for hemoglobin S (SCD-SS) or with both sickle and β-zero-thalassemia mutations (SCD-S β0-thalassemia) compared with those with trait or heterozygous mutation. Several studies have evaluated the best management strategies for SCD patients undergoing surgical procedures. One of the recommendations is to correct anemia by giving RBC transfusion or exchange transfusion before surgery. One study evaluated liberal strategy, where patients were transfused to maintain HbS concentration less than 30% compared with a conservative approach for transfusion in which Hgb is maintained at 10 g/dL, and authors found no difference in complication rates between the 2 strategies.[74] One of the oldest studies in this area is The Cooperative Study of Sickle Cell Disease that observed 3765 patients between 1978 and 1988 with a mean follow-up of 5.3 plus minus 2.0 years.[75] This study showed that peri-operative transfusions in SCD patients reduced the risk of sickle cell related complications. The Transfusion Alternatives Preoperatively in Sickle cell disease study (TAPS Study) was a randomized trial of 70 patients with SCD-SS or SCD-S

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Table 3
Landmark randomized clinical trials evaluating Hgb threshold for transfusion

Authors/Trial	Hgb Threshold in G/dL (Conservative Group)	Hgb Threshold in G/dL (Liberal Group)	Patient Population/Setting	Number of Patients	Primary Outcome	Outcome Liberal vs Restrictive
Hebert et al,[55] 1999 TRICC	7	10	MICU	838	30-d mortality	Unchanged
Lacroix et al,[56] 2007 TRIPICU	7	9.5	PICU	637	28-d mortality or multiorgan dysfunction	Unchanged
Hajjar et al,[57] 2010 TRACS	8	10	Cardiac surgery	502	30-d mortality and severe morbidity	Unchanged
Carson et al,[58] 2011 FOCUS	8	10	Elderly hip fracture	2016	60-d mortality or inability to walk 10 ft	Unchanged
Villanueva et al,[59] 2013	7	9	Severe GI Bleeding	921	45 d rate of death	Worse in Liberal
Holst et al,[60] 2014	7	9	Septic shock	1005	90 d mortality	Unchanged
Robertson et al,[61] 2014	7	10	Traumatic Brain Injury	200	Neurologic recovery at 6 mo	Increased adverse events in liberal group
Jairath et al,[62] 2015 TRIGGER	8	10	GI bleeding	936	28-d mortality or further bleeding	Unchanged
Murphy et al,[63] 2015 Titer2	7.5	9	Cardiac surgery	2007	Ischemia or infection within 3 mo	Unchanged
Mazer et al,[64] 2017; Mazer et al,[65] 2018 TRICS III	7.5	9.5	Cardiac surgery	5243	28 d and 6-mo composite mortality, MI, stroke, or new renal failure needing dialysis	Unchanged

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Garg et al,[66] 2019 TRICS III AKI Substudy	7.5	9.5	Cardiac surgery	4531	Perioperative AKI within 7 d of surgery	Unchanged
Ducrocq et al,[67] 2021 REALITY	8	10	Acute MI with anemia	668	Major adverse cardiovascular outcome	Unchanged
Carson et al,[68] 2023 MINT	7/8	10	Acute MI and anemia	3504	30-d Recurrent MI or death	Liberal transfusion did not significantly reduce outcomes.
Mullis et al,[69] 2024	5.5	7	Asymptomatic musculoskeletal injured trauma patients (age 18–50) who are no longer in the initial resuscitative period.	65	Postoperative infection, other post-operative complications, and Musculoskeletal Functional Assessment scores	Lower infection rate. Similar functional outcomes at 6 mo or 1 y.

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β0-thalassemia evaluating preoperative transfusion strategy for low or medium risk surgeries and found a reduced risk of post-operative complications in persons with SCD-SS undergoing medium risk surgery when their preoperative hemoglobin level was increased to 10 g/dL.[76] Additionally, without pre-operative transfusion, the need for peri-operative transfusion was increased in patients with SCD.[76]

The risks of transfusion in SCD include hyper viscosity and increased sickling from over-transfusion, hemolytic and non-hemolytic transfusion reactions, and transmission of infection. An updated Cochrane review in 2020 concluded that there is insufficient evidence from randomized trials to determine whether conservative pre-operative RBC transfusion is as effective as aggressive pre-operative RBC transfusion in preventing disease or surgery related complications in people with SCD.[77] Current consensus in both US[78] and United Kingdome[79] supports pre-operative RBC transfusion in patients with SCD who are undergoing elective surgeries. The American College of Hematology recommends that the decision-making should be individualized based on genotype, the risk level of surgery, baseline total Hgb, complications with prior transfusions, and disease severity. The task force favors pre-operative transfusion in surgeries requiring general anesthesia and lasting more than 1 hour and a goal Hgb of greater than 9 g/dL is favored.[78] The British Society of Hematology task force also recommends pre-operative transfusion in SCD patients undergoing medium- to high-risk surgeries for a goal Hgb of 10 g/dL.[79]

The authors recommend ensuring that the patients are normothermic, euvolemic, have normal oxygenation, and appropriate pain control. Also, folic acid replacement must be continued peri-operatively. As in other clinical contexts, optimization of hematinic substrates is appropriate with caution to avoid development of secondary hemosiderosis. Patients undergoing medium- to high-risk surgery should have pre-operative hemoglobin optimized to 10 g/dL and a multidisciplinary approach between hematology, blood bank, anesthesia, primary care physician, hospitalist, and surgeon is recommended.

Jehovah Witness and Patients in Whom Blood Is Not an Option

A very challenging situation in the peri-operative setting is the care of patients who refuse blood products transfusion for personal or religious beliefs, of which Jehovah's Witnesses are the most commonly encountered patient examples. There are over 8 million Jehovah's witnesses worldwide and their belief command its followers to abstain from blood transfusions or accepting other blood products even if there is a threat to their life. This can provide both ethical and clinical challenges in peri-operative care and, therefore, pre-operative optimization of anemia and coagulation status, as well as minimizing blood loss is of utmost importance. Although Jehovah's Witnesses do not accept autologous blood donation, they will accept blood if it is retained within a closed circuit, such as through cell salvage, acute normovolemic hemodilution, cardiopulmonary bypass, dialysis, and plasmapheresis. The authors recommend a clear discussion with patients and documentation about what they would accept.[80]

The optimization of anemia requires an appropriate evaluation of the hematologic disorders, with a focus on the immediately treatable conditions and may require multiple substrate supplementations (iron, folate, zinc, etc.) in addition to erythropoietic agents. Although, the optimization process should begin at least 6 weeks before surgery,[80] short-term optimization is possible as demonstrated in a randomized controlled trial in cardiac surgery, with simultaneous administration of IV iron, (20 mg/kg ferric carboxymaltose), erythropoietin (40,000 U subcutaneous erythropoietin alpha), parenteral cyanocobalamin (1 mg subcutaneous), and folic acid (5 mg p.o.) and consequent decreased post-operative transfusion requirements.[41] An important

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consideration in Jehovah witness patients is that erythropoietic agents should not contain human albumin; the agents darbepoetin alfa and epoetin alfa-epx are appropriate in this population.

There are multiple therapeutics approved to treat coagulopathy including antifibrinolytics (eg, tranexamic acid), recombinant factor VIIa, 4 factor prothrombin complex concentrates (4PCC), fibrinogen concentrates, and thrombopoietin receptor agonists.[81]

Post-operatively, minimizing laboratory tests, and using smaller (pediatric size) tubes for collection is recommended.[45,80,82]

INTRAVENOUS IRON IN PATIENT WITH INFECTIONS

The use of IV iron has been associated with increased risk for infections. However, iron deficiency and anemia are also associated with increased infection risk.[83] Limitations of the evidence include heterogeneity in clinical practice, as well as variability in reporting of infections as adverse clinical outcomes.[84]

Iron is a strong substrate for multiple bacteria, including *Escherichia coli, Klebsiella, Pseudomonas, Salmonella, Yersinia, Listeria, Staphylococcus, and Haemophilus influenzae*. The evidence of correlation between increased bacterial growth proportional and transferrin saturation comes from in vitro studies.[85]

A recent large systematic review and meta-analysis of 154 randomized controlled trials with 32,920 patients, aimed to examine the risk of infection associated with IV iron when compared with enteral iron or no iron. Intravenous iron was associated with a 17% increased risk of infections when compared to oral iron or no iron. IV iron was associated with increase in hemoglobin with a mean difference of 0.57 g/dL, and the risk of allogenic RBC transfusion was decreased by 7%. There was no meaningful effect of IV iron on mortality or LOS.[84]

Therefore, caution should be exercised when considering the use of IV iron in patients with severe infections, balancing the associated risk with allogeneic RBC transfusions. In the authors' practice, if source control has been established, the patient has been receiving appropriate antimicrobial therapy with demonstration of improvement in clinical features (eg, fever and hemodynamic status) and acute phase reactants (eg, C reactive protein, procalcitonin, etc.) then IV iron can be administered, especially for patients who refuse RBC transfusions.

PLASMA TRANSFUSION

Plasma is the component of whole blood that consists of protein C, protein S, antithrombin, albumin, tissue factor pathway inhibitor and the coagulation factors.[86]

Although plasma is overused as a blood product worldwide, being transfused in up to 1% of all hospitalized patients, the evidence supporting its appropriate use is insufficient. In the US, the overuse of plasma includes its transfusion for International normalized ratio (INR) less than 1.8, with up to 22.5% of patients receiving it for INR less than 1.6. Of note, the appropriate dosing for plasma is based on body weight and is 10 mL/kg to 20 mL/kg; this dose augments the concentration of coagulation factors by 20%; therefore, subtherapeutic doses are clinically ineffective, yet carry the risk associated with transfusion like transfusion associated circulatory overload.[87]

In the periprocedural setting, its most common utilization is for treatment of coagulopathy in actively bleeding patients, as well as for pre-operative optimization. Its most appropriate use is in the setting of active bleeding to treat significant deficiency of multiple coagulation factors. Warfarin reversal is a common scenario where plasma has been routinely used. However, currently there is preference for the use of vitamin K

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and 4PCC. In patients with bleeding because of vitamin K antagonists (warfarin) or vitamin K deficiency, plasma can be used when vitamin K or 4PCC are not immediately available.[87]

Other clinical scenarios where plasma is used include massive transfusion protocol and liver disease. Massive transfusion protocol (MTP) must be considered in patients undergoing surgeries with high bleeding risk. In MTP, a combination of plasma, red blood cells, and plasma is transfused at a ratio of 1:1:1 ratio. Nonetheless, increased volume of plasma as compared with RBCs can cause decrease in hematocrit levels, as well as dilution of fibrinogen.[87]

Plasma transfusion when INR is less than or equal to 2 is not supported by evidence because of lack of improvement of outcomes or laboratories values. In addition, there should be awareness that the Prothrombin time (PT) or INR levels below 2.0 correlate with normal concentration (>30%) of most clotting factors, hence making plasma transfusions unnecessary.[88] In addition, the PT/INR value is not the sole indicator of the status of hemostasis or thrombosis in some populations, as can be demonstrated in patients with chronic liver disease, who have a balanced coagulation profile with a prothrombotic risk associated with plasma use.[89] Also, in the patients with liver disease, fresh frozen plasma (FFP) can cause volume expansion with consequent increase in portal pressure increasing the risk of variceal bleeding.[90]

The Society for Interventional Radiology guidelines has very conservative recommendations: for patients undergoing a low bleeding risk procedure (eg, central venous access, paracentesis, thoracentesis, etc.), is recommended INR less than or equal to a range of 2.0 to 3.0; the only indication for plasma use in these patients is if femoral arterial access is needed; in patients undergoing a high bleeding risk procedure (deep organ biopsy) the society recommends that the INR be less than 1.5 to 1.8.[91]

Caution must be held with the sole use of INR to assess coagulopathy, as it may not accurately reflect the current rate of thrombin generation and actual hemostasis.[92,93] Therefore, in addition to the INR, clinicians must have awareness of other tests to assess coagulopathy, especially, the viscoelastic tests, which include Thromboelastogram (TEG) and rotatory thromboelastometry (ROTEM), which have decreased inappropriate blood products transfused without adverse clinical outcomes.[94,95]

Recent strategies to allow for safer and easy to use plasma products, especially in environments with limited resources, has allowed to develop a newer plasma product – the lyophilized plasma (LyP) which has the benefit of room temperature storage, pathogen-reduction, and rapid reconstitution, with similar clinical effectiveness to FFP. It can also be partially reconstituted to 50% of the volume, conferring a similar hemostatic benefit with decreased transfused volume, although with obvious higher colloid osmotic pressure than FFP.[87]

PLATELET TRANSFUSION

An important element to consider before invasive procedures is the platelet count. However, clinicians must appraise certain aspects involving the assessment of periprocedural thrombocytopenia, as well as the challenges associated with platelet transfusion; platelets are expensive and often are not readily available; have a short half-life (must be used within 5 days); they are stored at room temperature, which increases the risk of bacterial contamination; they carry a high risk of transfusion reactions and alloimmunization; and clinician compliance with recommended transfusion thresholds is often not optimal.[96–98]

A unit of platelet (either as a pool of 5 concentrates from different donors with same ABO group and Rhesus factor diluted in plasma or obtained directly from apheresis)

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Table 4
Current platelet thresholds recommended for transfusion by the Association for the Advancement of Blood & Biotherapies,[98] the British Committee for Standards in Haematology[102] and the Society for Interventional Radiology[91]

Society	Platelet Threshold	Indications
AABB/BSH	$\leq 10 \times 10^9$/L	Decrease spontaneous bleeding.
AABB/BSH	$< 20 \times 10^9$/L	Central venous catheter
AABB	$< 50 \times 10^9$/L	Lumbar puncture (AABB)
BSH	$< 40 \times 10^9$/L	Lumbar puncture (BSH)
AABB/BSH	$< 50 \times 10^9$/L	Major elective surgery
AABB/BSH	$< 100 \times 10^9$/L	Neurosurgery and ophthalmology
SIR	$< 20 \times 10^9$/L	Percutaneous procedures with low risk of bleeding: lumbar puncture, chest tube, central venous catheter, paracentesis/thoracentesis, etc.
SIR	$< 50 \times 10^9$/L	Percutaneous procedures with high bleeding risk: arterial access from femoral artery, deep organ biopsy, deep organ abscess drain, etc.

increase the circulating platelet number by 20 cells/μL to 30,000 cells/μL.[99] Platelets in the United States (US) are treated with a photochemical process with ultraviolet light that inactivates pathogens, as well as residual leukocytes, decreasing the risk of graft-vs-host disease and increase its storage life from 5 days to 7 days. However, this process significantly raises the cost associated with platelet transfusion.[100]

Clinicians must have awareness of 3 main conditions that can be associated with periprocedural thrombocytopenia. Pseudothrombocytopenia occurs when platelets aggregate in ethylenediamine tetraacetic acid-anticoagulated blood, and this can be assessed with direct microscopy of a RBC smear, or with measurement of platelet count with a citrate-anticoagulated blood. Hemodilution from the use of crystalloids and plasma can also decrease the circulating number of platelets. A third cause is consumption of platelets, in the setting of activation of coagulation cascade secondary to bleeding, inflammation, sepsis, and so forth.[101] Another condition that can occur is the development of heparin induced thrombocytopenia. The autoimmune conditions associated with thrombocytopenia often present as already identified underlying comorbid conditions, rather than a newly developed condition.

The current thresholds for platelet transfusion recommended by the AABB,[98] the British Committee for Standards in Haematology (BSH)[102] guidelines, and the Society

Table 5
Elements that contribute to coagulation effectiveness and thrombopoiesis

Mechanism	Recommendation
Improve endothelial function	Treat sepsis
Enhance platelet adhesion	Use desmopressin to increase circulating levels of von Willebrand factor
Optimization of coagulation factors	Use of recombinant factor VIIa Fibrinogen
Prevent fibrin degradation	Use of antifibrinolytics (tranexamic acid and aminocaproic acid)
Enhance thrombopoiesis	Use thrombopoietin receptor agonists (romiplostim, eltrombopag, avatrombopag, etc.)

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for Interventional Radiology (SIR)[91] can be seen in **Table 4**. The recommendation is transfusing single apheresis unit or equivalent.

An important consideration in the periprocedural setting is when platelets are not available, or when patients refuse platelet transfusion. In this context, the optimization of all elements of coagulation, as well as of thrombopoiesis are paramount (**Table 5**).

In addition to platelet count, especially in the setting of active bleeding and concerns for coagulopathy, viscoelastic testing also offers an accurate perspective to guide optimization of coagulation function.[94,95]

SUMMARY

Peri-operative anemia is highly prevalent and remains an independent predictor for post-operative mortality and morbidity. Pre-operative evaluation should focus on identifying the cause of anemia and optimization strategies should focus on increasing red cell mass and correcting any nutritional deficiencies. IV iron is safe and can be used for correcting pre-operative and post-operative anemia, especially when IDA is present. Benefit of IV iron in reducing transfusion or mortality remains controversial. Multiple randomized trials have shown non-inferiority of restrictive strategies for RBC transfusion in surgical patients, and the authors support this approach. Indiscriminate use of plasma or FFP is not supported by current evidence and care should be taken to avoid volume overload when using plasma. INR should not be used as the sole measure of coagulopathy when considering reversal strategies as it may not accurately reflect thrombin generation and actual hemostasis.

DISCLOSURE

None.

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